IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No: 37974-0156

Applicant: Bernhard FISCHER *et al.*

Appl. No.: To be assigned

Filing Date: Concurrently herewith

Title: STABLE FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please enter the following amendments.

IN THE SPECIFICATION

Page 1, following the title, please insert the following:

-- This application is a divisional of U.S. Serial No. 09/142,768, filed November 6, 1998, which is a 371 of PCT/AT97/00055, filed March 13, 1997. The entire contents of each of the above-identified applications are hereby incorporated by reference. --

IN THE CLAIMS

Please cancel claims 1-18 and 20-43 without prejudice or disclaimer and add the following claims:

44. (New) A method of recovering stable Factor VIII/vWF-complex from a protein solution that also contains contaminating proteins, wherein the method comprises

binding the Factor VIII/vWF-complex contained in the protein solution to an anion exchanger;

selectively eluting the contaminating proteins with an eluting agent containing a salt concentration of $\leq$ 200 mM and $CaC1_2$; and subsequently recovering Factor VIII/vWF-complex from the anion exchanger at a salt concentration of between $\geq$ 200 and $\leq$ 400 mM.

45. (New) The method according to claim 44, wherein the contaminating proteins are plasma proteins.

46. (New) The method according to claim 45, wherein the plasma proteins are selected from the group consisting of Vitamin K-dependent Factors, plasma proteases, fibronectin and fibrinogen.

47. (New) The method according to claim 44, wherein the $CaCl_2$ is contained in the eluting agent at a concentration of between 1 mM and 15 mM.

48. (New) The method according to claim 44, wherein the $CaC1_2$ is contained in the eluting agent at a concentration of 10 mM.

49. (New) The method according to claim 44, wherein the eluting is carried out at a pH of 6.0 to 8.5.

50. (New) The method according to claim 44, wherein the eluting is carried out at a pH of 7.4.

51. (New) The method according to claim 44, wherein the salt contained in the eluting agent is NaCl.

52. (New) The method according to claim 44, wherein a Factor VIII/vWF-complex containing high-molecular vWF multimers is obtained, and the Factor VIII/vWF-complex is free from low-molecular vWF molecules and from vWF degradation products.

53. (New) The method according to claim 44, further comprising subjecting the Factor VIII/vWF-complex recovered from said anion exchanger to a further chromatographic step.

54. (New) The method according to claim 53, wherein the further chromatographic step is affinity chromatography.

55. (New) The method according to claim 54, wherein the affinity chromatography is heparin chromatography carried out with a heparin affinity carrier

by binding the Factor VIII/vWF-complex from the protein solution to the heparin affinity carrier in a buffer system and recovering the Factor VIII/vWF-complex at a salt concentration of between $\geq$ 200 and $\leq$ 300 mM.

56. (New) The method according to claim 55, wherein the heparin affinity carrier is selected from the group consisting of AF-Heparin Toyopearl® (Tosohaas), Heparin EMD-Fraktogel® and Heparin-Sepharose Fast Flow®.

57. (New) A method of recovering a stable Factor VIII/vWF-complex comprising

subjecting Factor VIII or a Factor VIII/vWF-complex to a chromatographic treatment so as to provide a purified Factor VIII or Factor VIIII/vWF-complex;

admixing a purified high-molecular fraction of vWF molecules to the purified Factor VIII or Factor VIII/vWF-complex so as to provide a Factor VIII/vWF-complex having a molar ratio of Factor VIII to vWF of between 0.01 and 100.

58. (New) The method according to claim 57, wherein the molar ratio of Factor VIII to vWF is between 0.05 and 1.

59. (New) The method according to claim 57, wherein the purified Factor VIII or Factor VIII/vWF-complex is recovered from a plasma fraction.

60. (New) The method according to claim 57, wherein the purified Factor VIII or Factor VIII/vWF-complex is obtained from a cell culture supernatant derived from transformed cells, and the cell culture supernatant is free from cells.

61. (New) The method according to claim 57, wherein the purified high-molecular fraction of vWF molecules contains plasmatic vWF.

62. (New) The method according to claim 57, wherein the purified high-molecular fraction of vWF molecules contains recombinant vWF.

63. (New) The method according to claim 57, wherein the high-molecular fraction of vWF molecules has a specific platelet agglutination activity of at least 50 U/mg vWF:Ag.

REMARKS

Applicants have canceled claims 1-18 and 20-43 without prejudice or disclaimer of the subject matter recited therein, and applicants expressly reserve all rights to such subject matter. Applicants have added claims 44-63. Upon entry of this amendment, claims 19 and 44-63 will be pending. Applicants request examination of the claims. A first office action on the merits is awaited.

Respectfully submitted,

May 7, 2001
Date

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